Kidney International, Vol. 30 (1986), pp. 299–303

LABORATORY INVESTIGATION

Dietary protein prior to renal ischemia dramatically affects postischemic kidney function

PETER M. ANDREWS and SALLY B. BATES

Department of Anatomy, Georgetown University Medical Center, Washington, D.C., USA

Dietary protein prior to renal ischemia dramatically affects postischemic kidney function. Male Sprague–Dawley rats were maintained on high protein (60%), normal protein (20%), low protein (5%), or no protein (0%) diets for two or four weeks prior to 45 minutes of renal ischemia induced by renal pedicle clamping. Most (93%) of the rats on the high protein diet died within three days following renal ischemia. In addition, 69% of the rats on normal protein diets also died, most before the fourth day following ischemic insult. In contrast, 88% of the rats on the low protein diet lived, although some exhibited elevated serum creatinine levels for up to one to two weeks following ischemia. Finally, all of the rats on no protein diets lived, and most (75%) exhibited normal serum creatinine levels by the fourth day following ischemia. Shifting the diets of high protein and normal protein adapted rats to no protein diets immediately following ischemia did not improve postischemic survival. Also, changing the diets of no protein adapted rats to high protein diets immediately following ischemia did not significantly affect postischemic recovery. When rats were maintained on no protein diets for shorter periods of time prior to ischemia, it was found that approximately a week on this diet is necessary to provide maximum protection from postischemic acute renal failure. These findings demonstrate a dramatic effect of dietary protein prior to ischemic induced acute renal failure, and suggests that preoperative dietary protein intake should be an important consideration in those situations which are predisposed to postoperative acute renal failure.

Acute renal failure (ARF) resulting from renal ischemia remains an important complication of urologic or vascular surgery. Depending upon the severity of the ischemic insult, the result may be either temporary or irreversible acute renal failure, necessitating prolonged maintenance on hemodialysis units. Thus far we and others have concentrated on evaluating the effects of intravenous pretreatment with various compounds and developing surgical and hypothermic procedures to reduce the effects of renal ischemia [1–3]. Although dietary considerations following ischemia have been studied [4–11], the possible effects of diet prior to ischemic insult have not been adequately investigated. In the present investigation, we have used a renal pedicle clamping model in a control population of rats to demonstrate that preconditioning to different concentrations of dietary protein prior to renal ischemia will dramatically affect recovery from the ischemic insult. Specifically, high protein diets will exacerbate the ischemic insult while restricted protein diets will protect from renal ischemia.

Received for publication June 25, 1985
and in revised form December 12, 1985

Methods

All the rats used in these studies were male Sprague–Dawley rats weighing between 200 and 300 g. In each experiment, animals were divided into groups and started on Ralston Purina Co. purified test diets. The diets were isocaloric (4.17 kcal/g) and contained equal amounts of mineral and vitamin supplements. Dietary protein was adjusted by varying the amount of casein, a phosphoprotein derived from milk, to obtain 60%, 20%, 5% and 0% protein diets. Since the use of casein introduced additional phosphate into the protein diets, a 5% protein diet with added phosphate equivalent to that found in the 20% protein diet was also evaluated. Prior to induction of ischemia, the rats were weighed, 24 hour urine volumes collected in metabolic cages, and urine and blood (drawn from the tail vein) samples collected to evaluate urine and serum creatinine and protein levels. Creatinine values were determined using a Creatinine Analyzer 2 (Beckman Instruments, Fullerton, California, USA), serum protein measured using a protometer (National Instruments Co. Model # 100B), and urine protein measured using Albustix Reagent Strips (Ames).

In preparation for surgery, rats were anesthetized with Ketamine (60 mg/kg) administered intramuscularly followed by an intraperitoneal injection of sodium pentobarbital (21 mg/kg). A laparotomy was performed and the viscera reflected to expose the left kidney. The renal pedicle was then clamped using a 1.5 inch bulldog clamp (Roboz). The abdominal cavity was temporarily closed with wound clips, and the rats placed on a prewarmed heating pad. Following exactly 45 minutes of ischemia, the abdominal cavity was reopened and the bulldog clamp removed from the renal pedicle to permit reflow of blood to the kidney. A contralateral nephrectomy of the right kidney was then performed, the abdominal cavity sutured closed, and rats placed in comfortable cages with free access to their food and water. Daily blood samples were taken from tail veins in order to evaluate postischemic serum creatinine levels. Also, 48 hours following renal ischemia, the rats were placed in metabolic cages and their 24 hour urine volumes measured.

Three different series of experiments were performed in this investigation. In the first series, the postischemic renal function of rats was evaluated following two or four weeks on each of the special diets. In a second series, rats adapted to the high protein diet (60% protein) and normal protein diet (20% protein) were switched to a no protein (0% protein) diet immediately following the ischemic insult, while rats on a 0% protein diet were

Table 1. Renal function following two or four weeks on special diets

Diet	No. rats	Body wt change, *g*	Kidney wt/ body wt ratios $\times 10^2$	Average 24 hr urine volume, *ml*	Urinary protein *mg/dl*	Urine creatinine *mg/dl*	Serum creatinine *mg/dl*	Serum protein *g/dl*
2 Weeks On								
60% Protein	11	+55	0.45	32.3	60	37	0.5	6.5
20% Protein	12	+68	0.38	16.6	30	64	0.6	6.7
5% Protein	13	+20	0.35	8.4	30	73	0.6	5.9
0% Protein	9	−46	0.39	3.8	30	124	0.7	5.4
4 Weeks On								
60% Protein	4	+92	0.39	29.2	30	50	0.5	6.7
20% Protein	4	+113	0.36	8.4	30	132	0.6	7.3
5% Protein	4	+31	0.32	4.0	30	240	0.7	6.5
0% Protein	4	−80	0.40	3.2	30	186	0.6	5.4

Table 2. Postischemic percentage survival following 45 minutes ischemia

Diet	1	2	3	4	5	6	7	8	9	10	11	12	13	14
2 weeks on														
60% Protein	100	91	9	9	9	9	9	9	9	9	9	9	9	9**
20% Protein	100	100	92	58	58	42	42	42	42	42	42	42	42	42**
5% Protein	100	100	100	100	100	100	100	100	100	100	100	100	100	100
0% Protein	100	100	100	100	100	100	100	100	100	100	100	100	100	100
4 weeks on														
60% Protein	100	75	0	0	0	0	0	0	0	0	0	0	0	0*
20% Protein	100	100	75	0	0	0	0	0	0	0	0	0	0	0*
5% Protein	100	100	100	100	100	100	100	100	100	100	100	50	50	50
0% Protein	100	100	100	100	100	100	100	100	100	100	100	100	100	100
2 week pre/post diet														
60%/0%	100	100	0	0	0	0	0	0	0	0	0	0	0	0*
20%/0%	100	100	20	20	0	0	0	0	0	0	0	0	0	0*
0%/60%	100	100	100	100	100	100	100	100	100	100	100	100	100	100

Symbols are: * significantly less than values for 0% dietary group ($P < 0.01$, using chi square); and ** significantly less than values for both 0% and 5% dietary groups ($P < 0.01$, using chi square)

switched to a high protein diet (60% protein) immediately following ischemia. In a third series, the time period needed to obtain protection from renal ischemia by maintenance on a no protein diet was evaluated by placing rats on the 0% protein diet for either 2, 4, 6, 8, 10, 12 or 14 days prior to ischemia. Rats placed on a high protein diet (that is, 60% protein) for similar periods of time were run as controls along with the no protein dietary groups.

Results

Table 1 summarizes the effects of the four special diets on body weight, kidney/body weight ratios and renal function as determined by blood and urine creatinine levels, blood and urine protein levels, and 24 hour urine volumes. The rats maintained on high protein diets exhibited polyuria, a small increase in urinary protein, and some renal hypertrophy as indicated by the increased kidney/body weight ratios. Rats on the 0% protein diets exhibited oliguria, decreases in body weight, and hypoproteinemia. An evaluation of food consumption revealed that rats on 5% and 20% protein diets consumed nearly the same weight of food prior to ischemia. These two groups therefore, were equivalent to pair-fed groups. Rats on the 0% and 60% protein diets, however, consumed 34% and 10% less food (by weight), respectively, than these other two groups. No difference was noted in the postischemic response of rats on 5% protein diets with ($N = 5$) and without ($N = 12$) additional phosphate (that is, an amount of phosphate equivalent to that found in the 20% protein diet). The results from these two groups are therefore combined in the observations below.

Within the first four days following 45 minutes of renal ischemia, there was a dramatic difference in survival between groups of rats on the 60% and 20% protein diets versus rats on the 5% and 0% protein diets (Table 2). All but one of the rats on 60% protein diets died within three days following ischemia. Rats on the 20% diet fared only slightly better, with most (63%) dying within four days following ischemia. Many of the animals in these groups exhibited oliguria 48 hours following ischemia, and their serum creatinine levels rose significantly prior to death (Table 3). In sharp contrast to these two groups, all of the rats on 0% protein diets survived; their 48 hour serum creatinine levels were significantly less than those of the rats on the 20% and 60% protein diets ($P < 0.05$), and most returned to within normal serum creatinine levels by the fourth day following ischemia (Tables 2 and 3). Also, 88% of the rats on the 5% protein diets survived, with only two deaths occurring on day 12 following ischemia in the four week dietary group (Table 2). The 5% protein diet adapted rats also exhibited elevated postischemic serum creatinine levels for a considerably longer time (that is, one to two weeks) than rats on 0% protein diets (Table 3). In general, there did not appear to be a dramatic difference between the postischemic response of two week and four week

Table 3. Renal function of different dietary groups following 45 minutes of renal ischemia

Diet	No. rats	Average 24 hr urine volumes 48 hours following ischemia, *ml*	Average daily serum creatinine values, *mg/dl* (±SEM)										
			1	2	3	4	5	6	7	8	10	12	14
2 weeks on													
60% Protein	11	6.8	4.2 (0.16)	6.1* (0.43)	3.1 (1.60)	1.5@ (0)	1.4@ (0)	N	N	N	N	N	N
20% Protein	12	13.5	4.9* (0.12)	6.6** (0.36)	7.5** (0.87)	5.2** (1.15)	2.5 (0.37)	1.8 (0.40)	1.2 (0.21)	N	N	N	N
5% Protein	13	5.5	4.9 (0.40)	4.8 (0.74)	3.4 (0.65)	1.9 (0.33)	1.4 (0.14)	1.1 (0.07)	N	N	N	N	N
0% Protein	9	5.4	3.6 (0.51)	3.5 (0.80)	3.1 (0.96)	2.1 (0.74)	1.5 (0.37)	1.1 (0.13)	N	N	N	N	N
4 weeks on													
60% Protein	4	0.4	4.9* (0.22)	7.4* (0.75)	D	D	D	D	D	D	D	D	D
20% Protein	4	3.9	5.5* (0.19)	8.4* (0.29)	10.6* (0.64)	D	D	D	D	D	D	D	D
5% Protein	4	2.0	5.7 (0.25)	8.2 (1.05)	8.8 (2.25)	8.4 (2.66)	8.0 (2.75)	7.4 (2.71)	6.0 (2.38)	5.2 (2.02)	3.6 (1.32)	N	N
0% Protein	4	7.7	3.6 (9.21)	2.3 (0.29)	1.0 (0.09)	N	N	N	N	N	N	N	N
60%/0%	5	1.0	4.7* (0.10)	6.9* (0.18)	D	D	D	D	D	D	D	D	D
20%/0%	5	0.3	4.2* (0.07)	6.3* (0.20)	8.5*@ (0)	9.5*@ (0)	D	D	D	D	D	D	D
0%/60%	5	15.2	2.5 (0.18)	1.5 (0.21)	1.1 (0.17)	N	N	N	N	N	N	N	N

Abbreviations and symbols are: D, All rats dead; N, normal values (that is, less than 1.0 mg/dl); *, Significantly higher than value for 0% dietary group ($P < 0.05$, using Student's *t*-test); **, Significantly higher than values for both 0% and 5% dietary groups ($P < 0.05$, using Student's *t*-test); and @, represents values for only one survivor.

Table 4. Preischemic and postischemic renal function of rats maintained on no protein diets for different periods of time

Days on diet	No. rats	Average 24 hr urine volumes, *ml*		Average Daily Serum Creatinine Values mg/dl (±SEM)								Daily survival (%) following ischemia						
		Before ischemia	48 hr after ischemia	0	1	2	3	4	5	6	7	1	2	3	4	5	6	7
2	5	8.7	0.3	0.7 (0.1)	4.8 (0.1)	7.5 (0.2)	9.1* (0.6)	9.2* (1.3)	7.4 (3.4)	6.8 (4.5)	N	100	100	100	80	40	40	20*
4	4	5.3	4.2	0.8 (0.1)	4.8 (0.4)	6.2 (1.6)	7.2 (3.0)	6.2 (5.1)	N	N	N	100	100	100	75	50	25	25*
6	5	2.5	4.5	0.8 (0.1)	4.7 (0.3)	4.9 (1.1)	3.2 (1.7)	2.7 (1.5)	1.9 (0.9)	1.4 (0.5)	N	100	100	100	100	100	100	100
8	4	3.3	3.4	0.9 (0.1)	3.9 (0.8)	3.8 (1.9)	2.3 (1.0)	1.3 (0.2)	N	N	N	100	100	100	100	100	100	100
10	5	3.4	3.3	0.7 (0.1)	4.2 (0.2)	2.5 (0.6)	1.2 (0.1)	N	N	N	N	100	100	100	100	100	100	100
12	4	2.1	2.0	0.6 (0.1)	4.1 (0.9)	5.3 (1.5)	2.0 (0.3)	1.2 (0.1)	N	N	N	100	100	100	100	100	100	100
14	4	2.0	4.8	0.7 (0.1)	3.0 (0.6)	2.0 (0.7)	1.2 (0.1)	N	N	N	N	100	100	100	100	100	100	100

Symbol is: *, significantly different than for rats conditioned on no protein diets for six days or longer (Using Student's *t*-test for serum creatinine values and chi square for % survival, $P < 0.05$). Abbreviation is: N, normal values (that is, less than 1.0 mg/dl).

adapted rats. Shifting the 60% and 20% protein diet adapted rats to a 0% protein diet following ischemia did not improve their recovery from ischemia (Tables 2 and 3). Also, shifting the diets of 0% protein diet adapted rats to 60% protein immediately following ischemia did not appear to impair their recovery from the ischemic insult. The latter group did, however, exhibit significant increases in 24 hour urine volumes due apparently to their change in diet (Table 3), and had a 5% weight gain by one week following ischemia, compared with a 10% weight loss exhibited by rats maintained on a 0% protein diet for one week following ischemia.

When maintained on a 0% protein diet for different periods of time prior to renal ischemia, a significant improvement in both renal function and survival was not seen until rats were conditioned on this diet for six days and longer (Table 4). All 22 rats in these latter groups survived and returned to normal serum creatinine levels within a week following renal ischemia (Table 4). As in the previous studies, all of 14 rats adapted to the 60%

protein diet (two rats at each period of 2, 4, 6 days, etc.) and run along with the above no protein groups died within four days following ischemia. Although rats maintained on no protein diets for periods of time shorter than six days (that is, 2 and 4 days) prior to ischemia exhibited somewhat longer postischemic survival times compared to the high protein dietary groups, 75 to 80% of these rats eventually died following the ischemic insult.

Discussion

This study has shown that preconditioning on restricted dietary protein in the form of casein for six days or longer will provide significant protection from subsequent renal ischemia. In our investigations, all but one of a total of 34 rats preconditioned to a high protein diet (that is, 60% protein) prior to ischemia died within three days following 45 minutes of ischemic insult. Also, 11 of 16 rats preconditioned to a normal protein diet (that is, 20% protein) died by the fifth day following ischemia. In sharp contrast, all rats placed on a no protein diet at least six days prior to renal ischemia survived (total of 50 rats), and most exhibited normal serum creatinine levels on or before the fourth day following ischemia. Also, 15 of 17 rats preconditioned to a low protein diet (5% protein) survived 45 minutes of renal ischemia, although some exhibited elevated serum creatinine levels for over a week following ischemia. At present we can only speculate regarding the possible mechanism or mechanisms responsible for these results. However, it is well known that high dietary protein will increase glomerular filtration rate and renal blood flow, while decreasing protein intake, especially for extended periods of time, will significantly decrease renal blood flow and glomerular filtration rates [11–16]. It is, therefore, possible that the decreased work load associated with restricted protein diets might render the nephron less susceptible to renal ischemia. However, there are many other possible adaptive renal, humoral, and systemic changes independent of renal changes which might have resulted in the effects observed in our investigation.

In the past there have been studies concerned with the possible beneficial effects of low protein diets supplemented with essential amino acids on patients and animals suffering from ARF [4–6, 8]. The rationale for using low protein diets following ARF has been to reduce uremic symptoms and yet supply nitrogen in a form which can be completely utilized in the synthesis of body protein [17]. Other studies, however, have not supported the use of low protein diets following ARF [7, 9, 10] and argue that increased catabolism associated with ARF necessitates higher protein requirements to ensure better nutritional status [10, 17, 18]. In the present investigation, the postischemic diet did not play a major role in the postischemic recovery of rats which had been adapted to either the 60%, 20% or 0% protein diets prior to ischemia. Even when rats on a normal protein diet were switched to a no protein diet immediately following renal ischemia, their postischemic renal recovery did not improve. Conversely, switching rats from no protein diets to high protein diets did not impair the recovery of these animals. We should note, however, that in nephrotoxic models of acute renal failure (that is, uranyl nitrate and gentamicin), we have found that increasing dietary protein immediately following the nephrotoxic insult will exacerbate subsequent acute renal failure [19, 20]. Also, it is difficult to speculate from our findings as to what effects a high or low protein diet might have on long-term kidney function of the apparently recovered rats.

In this investigation, variables other than the amount of dietary casein did not appear to play a major role in the response of rats to renal ischemia. In that the 5% and 20% dietary protein groups, each consumed the same amounts of food; these two groups were equivalent to pair-fed groups. Also, although both the 0% and 60% groups consumed less food than the 20% or 5% dietary groups, these former groups exhibited different responses to renal ischemia. In order to keep the diets isocaloric with respect to one another, additional sucrose had to be added to the restricted protein diets. Most evidence indicates that elevated dietary sucrose will, if anything, exacerbate renal function [21]. Therefore, sucrose appears to be an unlikely candidate for the observed protective effects of the restricted protein diets. Perhaps more important is the fact that casein is a phosphoprotein and, although controversial [21], excess phosphate has been implicated as a cause of renal dysfunction [22, 23]. Nevertheless, in our investigation, we found no detrimental effects of adding additional phosphate to the low protein diets. Finally, we should note that other sources of protein might have different effects than were observed for dietary casein in this investigation. It has been shown, for example, that different sources of protein (that is, soya, meat) have different effects on kidney glomerular filtration rates and renal blood flow [24]. Nevertheless, the findings reported in the present investigation, together with similar observations using uranyl nitrate [19] and gentamicin [20] models of acute renal failure, support the conclusion that conditioning to different amounts of dietary casein can dramatically affect the response to a variety of renal insults. It will remain for future investigations to determine the mechanisms underlying this phenomenon.

Our investigations raise many other questions regarding the protective effects of restricted protein diets. For example, although we found that less than a week on a restricted protein diet will provide considerable protection for young adult male rats from ARF, how this period of dietary adaptation relates to humans and such variables as sex and age is not known. Other questions needing to be addressed include what effect does dietary protein have on other renal insults, whether different kinds or sources of protein (such as meat, milk, soya) will elicit different effects, what are the mechanisms responsible for these effects, and exactly how much protection can be provided by restricted protein diets alone and when used in combination with other preoperative procedures (that is intravenous mannitol) designed to reduce the degree of postischemic ARF. Although these and other related questions will be addressed in the near future, our present findings indicate that dietary protein should be carefully controlled and considered in any future investigations of ARF.

Finally, our results should have an important impact on the current clinical approach in many surgical situations where postoperative ARF is a potential problem. For example, following open heart surgery, the incidence of renal failure has been reported to be over 30% depending upon the criteria used [25, 26]. When postoperative ARF is severe enough to require dialysis, the mortality rate is very high (70 to 100%) despite aggressive postoperative treatment to treat renal failure [25, 26, 27]. These facts have led Abel et al to suggest that efforts would

be better directed toward preventing postoperative ARF rather than its treatment once established [28]. The results of our investigation clearly show that dietary protein is a major contributing factor affecting the severity of postischemic acute renal failure. By restricting the dietary protein in patients prior to renal or cardiovascular surgery wherein acute tubular necrosis is a potential problem, there is a strong possibility that this change in diet would reduce the incidence of both the mild as well as the more severe incidences of postoperative ARF.

Acknowledgments

This investigation was supported by National Institutes of Health Grants AM31111 & AM31177.

Reprint requests to Dr. Peter Andrews, Department of Anatomy, Georgetown University School of Medicine, 3900 Reservoir Rd., N.W., Washington, D.C. 20007, USA.

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